

CLAIMS

1. An altered IGFBP-2 molecule able to effect binding of IGF-I or IGF-II with high affinity characterised in having an inhibited release of IGF on contact with extracellular matrix or exposure to a protease.
2. An altered IGFBP molecule of claim 1 wherein the IGFBP-2 molecule has an alteration in one or more amino acids of a first ECM binding sequence which spans amino acids 179-184 and comprises the sequence PKKLRP [SEQ ID No 1].
3. An altered IGFBP molecule as in either claim 1 or 2 wherein the altered IGFBP-2 molecule has an alteration in one or more amino acids of a second ECM binding sequence which spans amino acids 227-244 and comprises the sequence KHGLYNLKQCKMSLNGQR [SEQ ID No 2].
4. An altered IGFBP molecule as in claim 2 wherein the alteration in the first ECM binding sequence is selected from the group consisting of SEQ ID No 9, SEQ ID No 10, SEQ ID No 11, SEQ ID No 12 and SEQ ID No 13.
5. An altered IGFBP molecule as in claim 3 wherein the alteration in the second ECM binding sequence is selected from the group consisting of SEQ ID No 14, SEQ ID No 15, SEQ ID No 16, SEQ ID No 17 and SEQ ID No 18.
6. An altered IGFBP molecule as in claim 1 wherein the amino acid sequence is altered as one or both of K180A and K181A
7. An altered IGFBP molecule as in either claim 2 or 3 wherein the IGFBP-2 molecule has additionally an alteration of its amino acid sequence that enhances resistance to proteolysis by one or more proteases.

8. An altered IGFBP molecule as in claim 7 wherein the IGFBP-2 molecule has an amino acid sequence altered in the linker domain to provide resistance to said one or more proteases.
- 5 9. An altered IGFBP molecule as claim 7 having one or more amino acids deleted within the linker domain
10. An altered IGFBP molecule as claim 7 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.
11. An altered IGFBP molecule as in claim 7 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.
- 15 12. An altered IGFBP molecule as in claim 1 wherein the IGFBP-2 molecule additionally has an amino acid sequence altered to enhances resistance to proteolysis by one or more proteases.
13. An altered IGFBP molecule as in claim 1 wherein the IGFBP-2 molecule has an amino acid sequence alteration in the linker domain to provide resistance to said one or more proteases.
14. An altered IGFBP molecule as claim 1 having one or more amino acids deleted within the linker domain
- 25 15. An altered IGFBP molecule as claim 1 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.
- 30 16. An altered IGFBP molecule as in claim 1 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.

17. An altered IGFBP molecule as in claim 13 wherein the amino acid sequence is altered at one or both positions as follows K180A and K181A.
18. A nucleic acid encoding an altered IGFBP-2 molecule said altered IGFBP
5 molecule able to effect binding of IGF-I or IGF-II with high affinity characterised in having an inhibited release of IGF on contact with extracellular matrix or exposure to a protease.
19. A nucleic acid encoding an altered IGFBP molecule as claim 18 wherein the
10 IGFBP-2 molecule has an alteration in one or more amino acids of a first ECM binding sequence which spans amino acids 179-184 and comprises the sequence PKKLRP [SEQ ID No 1]
20. A nucleic acid encoding an altered IGFBP molecule as in either claim 18 or 19
15 wherein the altered IGFBP-2 molecule has an alteration in one or more amino acids of a second ECM binding sequence which spans amino acids 227-244 and comprises the sequence KHGLYNLKQCKMSLNGQR [SEQ ID No 2].
21. A nucleic acid encoding an altered IGFBP molecule as in claim 19 wherein the
20 alteration in the first ECM binding sequence is selected from the group consisting of SEQ ID No 9, SEQ ID No 10, SEQ ID No 11, SEQ ID No 12 and SEQ ID No 13.
22. A nucleic acid encoding an altered IGFBP molecule as in claim 20 wherein the
alteration in the second ECM binding sequence is selected from the group consisting of
25 SEQ ID No 14, SEQ ID No 15, SEQ ID No 16, SEQ ID No 17 and SEQ ID No 18.
23. A nucleic acid encoding an altered IGFBP molecule as in claim 18 wherein the
amino acid sequence is altered in one or both of K180A and K181A
- 30 24. A nucleic acid encoding an altered IGFBP molecule as in either claim 19 or 20
wherein the IGFBP-2 molecule has additionally an alteration of its amino acid sequence
that enhances resistance to proteolysis by one or more proteases.

25. A nucleic acid encoding an altered IGFBP molecule as in claim 24 wherein the IGFBP-2 molecule has an amino acid sequence alteration in the linker domain to provide resistance to said one or more proteases.

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26. A nucleic acid encoding an altered IGFBP molecule as claim 24 having one or more amino acids deleted within the linker domain

27. A nucleic acid encoding an altered IGFBP molecule as claim 24 wherein
10 substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.

28. A nucleic acid encoding an altered IGFBP molecule as in claim 24 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.

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29. A nucleic acid encoding an altered IGFBP molecule as in claim 24 wherein the IGFBP-2 molecule additionally has an amino acid sequence altered to enhance resistance to proteolysis by one or more proteases.

20 30. A nucleic acid encoding an altered IGFBP molecule as in claim 18 wherein the IGFBP-2 molecule has an amino acid sequence altered in the linker domain to provide resistance to said one or more proteases.

31. A nucleic acid encoding an altered IGFBP molecule as claim 18 having one or
25 more amino acids deleted within the linker domain

32. A nucleic acid encoding an altered IGFBP molecule as claim 18 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.

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33. A nucleic acid encoding an altered IGFBP molecule as in claim 18 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.

34. A nucleic acid encoding an altered IGFBP molecule as in claim 29 wherein the amino acid sequence is altered at one or both positions as follows K180A and K181A

5 35. A nucleic acid encoding an altered IGFBP molecule as in any one of claims 19 to 36 wherein the nucleic acid is a vector, the vector having nucleic acid operably linked with a control sequence including a promoter for transcription leading to expression of the altered IGFBP.

10 36. A host cell carrying a nucleic acid as in any one of claims 18 to 35.

37. A method of reducing IGF mediated proliferation of a population of cancerous cells, the method including the step of contacting the population of cells with an altered IGFBP as in any one of claims 1 to 17.

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38. The method of reducing IGF mediated proliferation of a population of cancerous cells as in claim 39 wherein the cancerous cells are selected from the group consisting of prostate, colon and breast cancer cells.

20 39. The method of reducing IGF mediated proliferation of a population of cancerous cells as in claim 37 wherein the cancerous cells are colon cancer cells.